

REMARKS

Status of the Claims

Claims 1 and 4-10 will be pending in the above-identified application upon entry of the present amendment. Claims 1, 5, and 8-10 have been amended. Claim 11 has been cancelled herein. Support for the recitations in claims 8-10 can be found in the present specification, *inter alia*, at pages 12-13, paragraph [0023]. Specifically, paragraph [0023] recites:

The method of detection of an antigen using the above-described labeled secondary antibody and the primary antibody immobilized on a detection area is now described.

At first, a method of preparing a sample used in the detection is described.

First, a buffer containing an antigen, such as PBS, is spotted on a primary antibody immobilized on a detection area, and with leaving at 4°C to room temperature for 5 minutes to 1 hour, the antigen and the primary antibody are allowed to react and the antigen is bound to the primary antibody.

Subsequently, 1 to 50 µl of a reagent containing a magnetic bead labeled secondary antibody in a bead concentration of 0.01% to 1% is dropped on the detection area, and with leaving at 4°C to room temperature for 5 minutes to 1 hour, the antigen bound to the primary antibody is allowed to react with the labeled secondary antibody. Then, unreacted secondary antibody is washed away with distilled water or the like to give a (labeled secondary antibody)-(antigen)-(immobilized primary antibody) sandwich structure.

In the present invention, detection is performed using a sample having such a sandwich structure immobilized on a detection area prepared as described above (emphasis added).

Accordingly, the step of binding the analyte to a labeled specific binding material to form a conjugate requires being left. In other words, this step is done without stirring. Thus, no new matter has been added. Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Examiner's Interview

Applicants would like to thank the Examiner for her time during the interview on December 23, 2009. Applicants appreciate the courtesies extended to them in this application. Applicants believe that the claims are now in condition for allowance. Should the Examiner believe that there remains any outstanding issues, Applicants respectfully request that the Examiner contact Applicants' Representative so as to expedite resolution of these outstanding issues, via an Examiner's Amendment or the like.

Issue under 35 U.S.C. § 103(a)

1) Claims 1, 4, 6, and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Josephson et al. '029 (US 2003/0092029) in view of Rohr '970 (US 5,445,970) and further in view of Thompson '304 (US 2003/0190304).

2) Claims 5 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Josephson et al. '029 in view of Rohr '970 and Thompson '304 and further in view of Foster '879 (US 4,444,879).

Applicants respectfully traverse. Reconsideration and withdrawal of these rejections are respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

MPEP 2141 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors are:

- (a) determining the scope and content of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating any evidence of secondary considerations.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner has to provide some rationale for determining obviousness. MPEP 2143 sets forth some rationales that were established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

As the MPEP directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. See MPEP 2143.03.

Distinctions over the Cited References

Independent claims 1 and 8 recite the element “a magnetic bead having a diameter of 0.5 to 10 μm .”

As the Examiner admits, the Josephson et al. ‘029 reference fails to disclose this limitation. However, the Examiner relies on Rohr ‘970 to overcome this deficiency. Specifically, the Examiner alleges that Rohr ‘970 discloses magnetic particles having a size range between 0.01 to 10 μm .

According to MPEP 2143.01, the combination of references cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose. Josephson et al. ‘029 disclose that the overall size of the nanoparticles is less than about 1-100 nm. Thus, the particles disclosed in Josephson et al. ‘029 must be nanoparticles with a diameter of less than about 1-100 nm for the reference to be operable for its intended purpose. Thus, the references cannot be properly combined.

In other words, one of ordinary skill in the art would not combine Rohr ‘970 with Josephson et al. ‘029 since Josephson et al. ‘029 specifically recite the desired size of the nanoparticles. Therefore, a *prima facie* case of obviousness has not been established, and withdrawal of the outstanding rejection is respectfully requested.

With specific respect to independent claim 8, the claim recites the step of “binding the antigen to a labeled specific binding material, *without stirring*, to form a conjugate” (emphasis added).

Regarding the selection of the diameter of the magnetic particles, Rohr '970 recites:

Generally, small magnetic particles with a mean diameter of less than about 0.03 μm (300 Å) can be kept in solution by thermal agitation and do not spontaneously settle.... Generally, large magnetic particles having a mean diameter greater than about 10 microns can respond to weak magnetic fields. Although large or dense labels may be used, such labels may require that the reaction mixture be stirred or agitated during the incubation steps to inhibit settling of the particles. In another embodiment, the magnetic particles can be selected to remain dispersed in the reaction mixture for a time sufficient to permit the required binding reactions without the need for a stirring or mixing means (col. 13, lines 7-25).

This recitation indicates that the small magnetic particles with a mean diameter of less than about 0.03 μm do not require being stirred because they do not spontaneously settle. However, the large magnetic particles require being stirred in order to inhibit the settling of the particles. *The reason why the stirring for the purpose of inhibiting the settling of the particles is required is because the settling of the particles does not cause reactions.*

In such circumstances, although Rohr '970 discloses the magnetic particles with a diameter of a range of about 0.01 μm to about 1,000 μm , the magnetic particles which do not really require being stirred are limited to the small magnetic particles with a diameter of a range of 0.01 μm to 0.03 μm . In other words, if one of ordinary skill in the art uses magnetic beads having a diameter of 0.5 to 10 μm , required in the labeled specific binding material of the present invention in view of Rohr '970, one of ordinary skill in the art would expect that they must be stirred in order to inhibit the settling thereof.

However, as disclosed in Example 2 of the present specification, 10 μl of the magnetic bead labeled antibody solution is spotted on the surface of a polystyrene plate where the antigen is immobilized. In such circumstances, since this sample has a small amount and is not stirred, the magnetic bead is expected to settle right after the spotting. However, the high reactivity can be really provided due to PEG spacer effects.

In other words, the present invention requiring a magnetic bead having a large diameter can provide high reactivity without using any stirring means. *The reason why a magnetic bead having a large diameter is used in the present invention is because magnetic signals sufficient for detection are generated.*

Thus, although the present invention uses a magnetic bead having a large diameter, which should settle if not stirred, the present invention can provide high reactivity without using any stirring means. As a result, the labeled specific binding material of the present invention can be also used for the detection of the samples in such a small amount that the stirring cannot be conducted, in spite of the use of a magnetic bead having a large diameter.

However, Josephson et al. '029 only disclose the magnetic particles with a small diameter of less than about 1-100 nm, which do not settle without using any stirring means.

Additionally, as described above, if one of ordinary skill in the art uses magnetic beads having a large diameter of 0.5 to 10 μm , required in the labeled specific binding material of the present invention in view of Rohr '970, one of ordinary skill in the art would expect that they must be stirred in order to inhibit the settling thereof.

Therefore, the above effects according to the present invention cannot be expected in view of Josephson et al. '029 and Rohr '970.

As discussed above, Josephson et al. '029 in view of Rohr '970 do not disclose each and every aspect of claim 1, from which all other claims ultimately depend. Applicants respectfully submit that Thompson '304 and Foster '879 do not overcome the deficiencies of these references.

To establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be disclosed by the cited references. As discussed above, the cited references fail to disclose all of the claim limitations of independent claims 1 and 8, and those claims dependent thereon. Accordingly, the combination of references does not render the present invention obvious.

Furthermore, the cited references or the knowledge in the art provide no reason or rationale that would allow one of ordinary skill in the art to arrive at the present invention as claimed. Therefore, a *prima facie* case of obviousness has not been established, and withdrawal of the outstanding rejections is respectfully requested. Any contentions of the USPTO to the contrary must be reconsidered at present.

CONCLUSION

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case clearly indicating that each of claims 1 and 4-10 are allowed and patentable under the provisions of title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Chad M. Rink, Reg. No. 58,258 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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